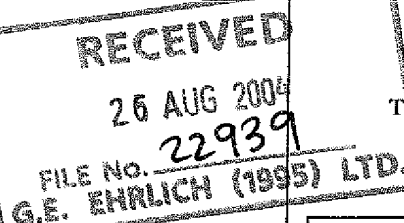


PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
GAL EHRLICH
G.E. EHRLICH (1995) LTD
28 BEZALEL STREET
RAMAT GAN, ISRAEL



PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 0122939	Date of Mailing (day/month/year) 13 AUG 2004
International application No. PCT/IL02/00174	International filing date (day/month/year) 05 March 2002 (05.03.2002)
Applicant YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALM	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 *bis*.1 and 90 *bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Stuart P. Baum
Stuart P. Baum

Telephone No. (571) 272-1600

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 0122939	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/IL02/00174	International filing date (<i>day/month/year</i>) 05 March 2002 (05.03.2002)	(Earliest) Priority Date (<i>day/month/year</i>) 05 March 2001 (05.03.2001)
Applicant YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALM		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (See Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL02/00174

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-45, including SEQ ID NO:1 and 2

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL02/00174

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 12/29, 15/82, 5/04, 15/29; A01H 5/00
 US CL : 536/23.1, 23.6, 24.1, 24.3; 435/468, 419; 800/278

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 23.6, 24.1, 24.3; 435/468, 419; 800/278

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 WEST, STN: agricola, biosis, caplus, caba; sequence search SEQ ID NO:1 and 2, DNA encoding SEQ ID NO:2

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---	EP 0 774 512 A2 (IMANAKA, TADAYUKI) 21 May 1997 (21.05.1997), entire document.	1, 6, 9, 10-14
Y ---		2-5, 16-21, 24-29, 31-36, 39-44
Y ---	SOTO, A. et al. Heterologous expression of a plant small heat-shock protein enhances Escherichia coli viability under heat and cold stress. Plant Physiology. June 1999, Vol. 120, pages 521-528, entire document.	15, 30, 45
A ---		1-6, 9-14, 16-21, 24-29, 31-36, 39-44
Y ---	LEE, G.J. et al. Structure and in Vitro molecular chaperone activity of cytosolic small heat shock proteins from pea. J. Biological Chemistry. 05 May 1995, Vol. 270, No. 18, pages 10432-10438, entire document.	15, 30, 45
A ---		1-6, 9-14, 16-21, 24-29, 31-36, 39-44
A	NCBI database for nucleotide sequences, National Center for Biotechnology Information, National Library of Medicine, NIH (Bethesda, MD, USA) BRADSHAW, H.D. et al., Accession Number M18538, 30 November 2000, encodes a protein that is 99.5% identical to SEQ ID NO:2.	7-8, 22-23, 37-38

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
06 August 2004 (06.08.2004)	13 AUG 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	Authorized officer Stuart F. Baum
Facsimile No. (703) 305-3230	Telephone No. (571) 272-1600

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-45, drawn to an isolated nucleic acid comprising a first polynucleotide encoding a boiling stable protein, or a detergent stable protein or a protease resistant protein and a second polynucleotide comprising a promoter operably linked to the first polynucleotide or wherein the first polynucleotide has a 60% sequence identity with SEQ ID NO:1, and wherein said stable protein has a sequence at least 60% identical to SEQ ID NO:2 and a method of isolating a nucleic acid encoding a boiling stable protein, or a detergent stable protein or a protease resistant protein comprising screening an expression library.

Group II, claim(s) 1-45, drawn to an isolated nucleic acid comprising a first polynucleotide encoding a boiling stable protein, or a detergent stable protein or a protease resistant protein and a second polynucleotide comprising a promoter operably linked to the first polynucleotide or wherein the first polynucleotide has a 60% sequence identity with SEQ ID NO: 5, 6, 34, 39, or 40 and wherein said stable protein has a sequence at least 60% identical to SEQ ID NO:2 or 35 and a method of isolating a nucleic acid encoding a boiling stable protein, or a detergent stable protein or a protease resistant protein comprising screening an expression library.

IF APPLICANT ELECTS GROUP II, APPLICANT IS ALSO TO ELECT ONE NUCLEIC ACID SEQUENCE AND ONE CORRESPONDING AMINO ACID SEQUENCE AS RECITED IN GROUP I. APPLICANTS HAVE THE OPTION TO PAY AN ADDITIONAL \$210.00 FOR EACH ADDITIONAL PAIR OF DNA AND AMINO ACID SEQUENCES.

Group III, claim(s) 46-50, 53-60, 63-70, 73-75 and 100-102 drawn to an isolated boiling stable, detergent stable or protease resistant polypeptide and a method of preventing an aggregating protein from aggregating comprising the elected polypeptide.

IF APPLICANT ELECTS GROUP III, APPLICANT IS ALSO TO ELECT ONE NUCLEIC ACID SEQUENCE AND ONE CORRESPONDING AMINO ACID SEQUENCE FROM THE BELOW LIST:

SEQ ID NO:1; SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:34; SEQ ID NO:39; SEQ ID NO:40; SEQ ID NO:2; SEQ ID NO:35.

APPLICANTS HAVE THE OPTION TO PAY AN ADDITIONAL \$210.00 FOR EACH ADDITIONAL PAIR OF DNA AND AMINO ACID SEQUENCES.

Group IV, claim(s) 51-52, 61-62, 71-72, drawn to an antibody.

Group V, claim(s) 76-77, and 103 drawn to a method of enriching or isolating a denaturant stable and/or protease resistant protein having chaperone-like activity.

Group VI, claim(s) 78-79, drawn to a method of isolating a gene encoding a denaturant stable and/or protease resistant protein having chaperone-like activity comprising microsequencing a protein, designing oligonucleotides and screening a library.

Group VII, claim(s) 80, drawn to a method of isolating a nucleic acid potentially encoding a denaturant stable and/or protease resistant protein comprising screening a cDNA or genomic library with a polynucleotide comprising at least 17 bases at least 60% identical to SEQ ID NO:1, 5, 6, 34, 39, 40.

IF APPLICANT ELECTS GROUP VII, APPLICANT IS ALSO TO ELECT ONE NUCLEIC ACID SEQUENCE AS RECITED IN GROUP VII. APPLICANTS HAVE THE OPTION TO PAY AN ADDITIONAL \$210.00 FOR EACH ADDITIONAL DNA SEQUENCE.

Group VIII, claim(s) 81, drawn to a method of isolating a nucleic acid potentially encoding a denaturant stable and/or protease resistant protein comprising searching an electronic library.

IF APPLICANT ELECTS GROUP VIII, APPLICANT IS ALSO TO ELECT ONE NUCLEIC ACID SEQUENCE FROM THE BELOW LIST:

SEQ ID NO:1; SEQ ID NO:2; SEQ ID NO:5-35;
SEQ ID NO:39-40.

APPLICANTS HAVE THE OPTION TO PAY AN ADDITIONAL \$210.00 FOR EACH ADDITIONAL DNA SEQUENCE.

INTERNATIONAL SEARCH REPORT

PCT/IL02/00174

Group IX, claim(s) 82, drawn to a method of isolating a nucleic acid potentially encoding a denaturant stable and/or protease resistant protein comprising using PCR.

IF APPLICANT ELECTS GROUP IX, APPLICANT IS ALSO TO ELECT ONE NUCLEIC ACID SEQUENCE FROM THE BELOW LIST:

SEQ ID NO:1; SEQ ID NO:2; SEQ ID NO:5-35; SEQ ID NO:39-40.

APPLICANTS HAVE THE OPTION TO PAY AN ADDITIONAL \$210.00 FOR EACH ADDITIONAL DNA SEQUENCE.

Group X, claim(s) 83, drawn to a method of detergent-free isolation of a protease-resistant protein.

Group XI, claim(s) 84-88, drawn to a fusion protein comprising a denaturant stable and/or protease resistant polypeptide and a method of immunization.

Group XII, claim(s) 89-90, drawn to a method of protecting an enzyme preparation from reduction in enzymatic activity.

Group XIII, claim(s) 91, drawn to a method of administering to an animal having an immune system a polypeptide.

Group XIV, claim(s) 92-94, drawn to a method of rendering a plant more tolerant to a biotic or abiotic stress and a transgenic plant, both of which, comprising expressing a denaturant stable and/or protease resistant protein.

Group XV, claim(s) 95-99, drawn to a methods of increasing cell migration, accelerating wound healing, inducing wound healing strengthening hair, nail or skin and grooming hair, nail or skin, all of which comprising exposing or administering an amount of a denaturant stable and/or protease resistant protein.

Group XVI, claims 105-106, drawn to a method of treating a disease associated with protein aggregation of an aggregating protein.

Group XVII, claims 107-108, drawn to a method of increasing a binding avidity of a binding molecule.

Group XVIII, claims 109-113, drawn to a hetero complex comprising an oligomer including a plurality of a denaturant stable and/or protease resistant protein.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.